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Simple and choice reaction times are prolonged following extracorporeal circulation: A potential method for the assessment of acute neurocognitive deficit

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Background:

Cognitive deficit related to open heart surgery came into the focus of interest according to professional and social expectations. The negative effects on quality of life and the large number of involved patients emphasize the need its investigation.

Material/Methods:

The bedside measurement of simple and choice reaction times (sRT and cRT) has the objectivity of cortical evoked potential analysis without the need for EEG instrumentation and laboratory. This is a functional assessment similar to neuropsychological tests, but requires a significantly shorter time and is less demanding for the patient.

Results:

Fifty patients who had undergone open heart surgery were investigated. Statistically significant positive correlation of sRT and cRT prolongation and perfusion time was found. At the same time there were no statistically significant changes in mean sRT and cRT values before (sRT: 208±54 s, cRT: 369±59 s) and after (sRT: 229±67 s, cRT: 392±105 s) the surgery, probably due to the inhomogeneous patient population. The weak correlation (coefficients: 0.1418–0.8484) for sRT and cRT changes as a function of perfusion time confirms the presence of other factors of postoperative brain damage.

Conclusions:

The investigated bedside test is clinically feasible, simple, and can be completed within 30 minutes. Further studies are encouraged to compare this method with other tests in a larger, stratified cardiac surgery population.

key words:

cognitive dysfunction • brain damage • open heart surgery • reaction time • P300 potential

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BACKGROUND

In Europe, approximately 650 open heart surgeries per million population were performed during the year 2000 [1]. Owing to improvements in cardiopulmonary bypass (CPB) techniques, operative practice, anesthesiology, and intensive care, the mortality and morbidity rates of cardiac surgery have decreased significantly since the first successful clinical application of CPB by Gibbon [2]. However, cerebral injury associated with CPB came into prominence according to medical and social expectations. Brain damage can range from mild neuropsychological (cognitive) deficit to serious and sometimes lethal ischemic brain lesions. Short-term cognitive impairment is observed in 33–83%, long-term cognitive injury in 20–60%, postoperative delirium in 10–30%, and stroke in 1.5–5.2% of cases after CPB [3–6]. Postoperative cognitive deficit, including deterioration of memory, attention, and motor speed, significantly impacts on the patients' quality of life despite an otherwise successful operation at 12 months [7,8] or even at 3 years compared with matched non-surgical controls [9]. CPB duration is a generally accepted risk-factor for morbidity and mortality [10]; however, its correlation with cognitive dysfunction is poorly investigated [11]. These facts emphasize the need for research, prevention, early recognition, and monitoring as well as treatment of post-CPB neurocognitive deficit.

The possible reasons for post-CPB brain injury include 1) decreased cerebral blood flow due to impaired autoregulation, persistent carotid artery disease or systemic hypoperfusion, 2) microembolism (bubbles, fat particles, platelet aggregates, plastic fragments from the tubing), 3) macroembolism (embolus from atherosclerotic plaque or intracardiac thrombus, debris from the operating area, massive air embolism), 4) systemic inflammatory response caused by the artificial material surfaces of the CPB circuit, and 5) metabolic (acid-base, carbohydrate) disorders. All of these factors, with the exception of macroembolism, may contribute to the most frequently occurring cognitive deficit (macroembolism causes more severe events) [3,5,12,13].

Preventive efforts may decrease the incidence of cognitive dysfunction following cardiac surgery. However, at this time a simple quantitative assessment of cerebral dysfunction is needed which can help to investigate the pathological background, facilitating its prevention, early detection, and the evaluation of the success of rehabilitation.

Current methods for the *in vivo* diagnosis of brain injury comprise physical, radiomorphological, functional, and biochemical examinations, although their simultaneous evaluation often shows discordance. Serious focal or diffuse lesions can be diagnosed by imaging techniques; however, their value in assessing cognitive dysfunction is rather limited. Recent studies demonstrated that the neurocognitive deficit after cardiac surgery is unrelated to acute cerebral ischemia detected by diffusion-weighted MRI [15]. The usefulness of biochemical markers released from the damaged brain tissue (protein S100, neuron-specific enolase) is controversial because of their low specificity due to disturbing factors related to CPB and surgical injury of other tissues; additionally, there is no information on the localization of the cerebral lesion [3,15]. Currently, the most suitable approach to studying neurocognitive disturbance

is functional assessment; neither morphological nor biochemical examinations are routinely used for these purposes in clinical practice. Functional investigation, especially neuropsychological tests, are determinant and may more closely coincide with the patient's postoperative quality of life. However, most of these examinations are demanding for the patient, especially in the early postoperative period, because they require the patient's constant attention for several hours, and they are time consuming for the staff as well. Electrophysiological examinations (e.g. cognitive evoked potentials) are also useful, reproducible, objective, and less time consumptive than neuropsychological tests [16–19], but they usually require a special EEG laboratory, and the postoperative transportation may also be exhausting for the patient [3]. A simple, reproducible, fast, but inexpensive bedside cognitive test is needed which can be repeated even every day for follow-up without fatigue to the operated patient. Reaction time measurements may keep the advantages of electrophysiological examination without the need for sophisticated instrumentation and a special environment, allowing cognitive assessment in a hospital room or intensive care unit.

Cognitive function evoked by auditory or visual (and other) stimuli is reflected in the brain potentials obtained by signal-averaged EEG (event-related potentials, ERP). Typical negative-going potentials are N100 and N200, occurring approximately 100 and 200 ms after the stimulus, respectively. Positive-going potentials are the P200 and P300, with a latency of approximately 200 and 300 ms, correspondingly. While the N100 and P200 (and P100) reflect sensory input-related processes [20–22], the N200 and P300 components are associated with stimulus evaluation, updating short-term memory, response selection (decision making), and reorientation of attention [20,23,24]. Their amplitude and latency depends on the probability, complexity, perception, and subjective meaning or importance of the stimulus, the individual's mental state, cognitive capability, personality, handedness, and hereditary factors, among others [24]. Therefore the prolongation of the N200 and P300 latencies may reflect the impairment of certain cognitive processes [24,25].

According to our previous study [26] and those of other authors [20,24,27–29], P300 is linked to the complex or choice reaction time (cRT), when the task should be achieved after target stimuli but not after more frequently occurring standard stimuli [30]. P300 evoked potentials were effectively used for brain function assessment during [19] and after [16,17] cardiac surgery or in hypothermic circulatory arrest [31]. Correlation of P300 and reaction time measurement was found in schizophrenic patients [20] and patients suffering stroke [29] and in healthy volunteers under hypoglycemic [27] and hypoxic [28] conditions. In our previous study [26], P200 temporally correlated with simple reaction time (sRT), in which a simple task (button press) must be executed as fast as possible after a given stimulus. However, Krull and colleagues found association of sRT and the amplitude of P100 [22]. Acute alcohol consumption slowed both sRT and cRT as well as P200 and P300 peaking in females [23].

Based on these data, we hypothesized that sRT and cRT measurement can be a feasible tool in detecting and screening cognitive dysfunction after open heart surgery. The aim of

the present investigation was to test our equipment and method in clinical circumstances and find the relationship between sRT and cRT versus extracorporeal perfusion time.

MATERIAL AND METHODS

Instrumentation

Special digital instrumentation and analyzer software were developed at our laboratory. The hardware contains a pseudorandom pulse-generator realized by a 12-bit shift register (assuring 4095 cycles without repeating the same sequence) that triggers a sound generator and a timer unpredictably in 600-ms to 10-s intervals. The sound generator synthesizes a 250-, 500-, or 1000-Hz sine wave with a 5-ms rise and fall time to be amplified for a standard binaural headphone to a calibrated intensity of 60 dB above the actual hearing threshold, which also can be determined with the system. The equipment with the PC is placed on a stainless steel trolley, assuring portability for bedside measurement.

During sRT measurement, the signal is turned off by the patient as fast as possible by pressing a button on a separate small hand-held unit (hand-unit) connected to the main unit by a flexible cable. The reaction time is measured by the timer in 0.5-ms resolution and is shown on a 3.5 digit 7-segment LED display in 1 ms rounded resolution, and a new cycle starts with zeroing the timer. When the timer overflows the 1500 ms limit without a button press, an error message is generated and a new cycle begins with restarting the timer. The start and stop signals are transmitted to the line-in connector of a sound card in the PC that also measures the time duration in 0.5-ms resolution and stores the data for further analysis. The number of cycles can be set to 32, 64, or 128.

The cRT measurement requires 6–8 times more standard signals of 250 Hz and 50-ms duration than target signals of 1000 Hz and 25-ms duration, after which a button-press should be done with the shortest latency (“oddball paradigm”). The cRT is the time duration between the begin of a target signal and the button-press. The new cycle begins with zeroing the timer. Timer overflow without button-press at 1500 ms or pressing the button after a standard signal generates an error message, restarts the timer, and the next cycle begins. Results are displayed and stored in the same way as for the sRT measurement. The number of target signal cycles can be set to 32, 64, or 128.

Patients and data acquisition

A total of 50 patients underwent open heart surgery (40 male and 10 female, mean age: 56.86 years, range: 41–73 years; 26 isolated coronary bypass grafting, 12 valve replacement or atrial septal defect closure, 12 combined operations) were enrolled in this study. All patients gave written informed consent to the examinations. The study was approved by the local ethics committee. Caffeine and alcohol consumption was not allowed for the patients 6 hours prior to the examination; patients on sedatives were not included. On the day before the operation and on one of the 3–5th postoperative days after audibility threshold examination, 64-64 sRT and 64-64 cRT values were acquired from each patient and analyzed off-line. The measurements were per-

formed in supine position in their beds at the ward of cardiac surgery. The patient was equipped with a commercial stereo headphone on the ears and a blinker on the eyes to exclude disturbing factors from the environment. The hand-unit was held in the patient’s dominant hand. The sRT examination lasted for about five minutes and a cRT-run took about 20 minutes. The reaction time series were stored on the hard disk of the PC in ASCII format. Besides demographical data, the type of the operation, the aortic cross-clamp time, the perfusion time, and any intra- or post-operative complications were also recorded.

Statistical analysis

The sRT and cRT series were considered to show an exponential distribution. The samples in the tail (extremely long reaction time values, outliers) may be the result of fault or deconcentration, but not reflecting reaction time; therefore the tail was reduced by eliminating these values with an iterative method in order to approximate a normal distribution. (The ratio of missed samples may also contain information on cognitive damage; it was not investigated in the study.) The λ parameter of the exponential distribution was estimated ($\frac{1}{\lambda} = \bar{x}$, the samples were assorted in an ascending series, and the tail-probability was calculated at every iteration: $q = e^{-\lambda \cdot x}$, where x is the maximum value of the actual sRT or cRT series. The procedure was stopped when $q < q_{\min}$ ($q_{\min} = 0.25$ was chosen empirically); otherwise the value was discarded and the cycle was restarted from estimating the λ parameter with the remaining samples until this rejection was necessary. The patient was rejected from the study if the number of discarded items was greater than five in either 64-element turn. The mean of the residual values was computed to get the preoperative and postoperative sRT and cRT at each patient. The median of pre- and post-operative reaction times were compared in women, men, and the total population by the Wilcoxon signed-rank test. Considering the relatively high inter-individual variation of the reaction times, the ratios of the post- and preoperative sRTs and cRTs (sRT_2/sRT_1 , cRT_2/cRT_1) were delineated as a function of total perfusion time and aortic cross-clamp time and their correlation and regression were analyzed by the BMDP software package (Statistical Solutions, Saugus, MA) [32]. The regression model was:

$$y = b_0 + b_{\text{cross}} \times \text{crossclamp time} + b_{\text{perf}} \times \text{perfusion time} \quad (1)$$

RESULTS

There were no important intra- or postoperative complications in the study. The mean cross-clamp time and its standard deviation were 62 ± 27 minutes and CPB time was 86 ± 32 minutes in the investigated population. All of the patients performed the test within 30 minutes. Only one patient was rejected because of a high portion of discarded reaction time values by iteration; for the other patients, no more than 3 items were removed from each epoch.

Correlation and linear regression analysis of sRT and cRT versus cross-clamp time and perfusion time was performed. The postoperative/preoperative sRT ratio is presented as a function of perfusion time separately for women and men and together in Figure 1 and the results of cRT measurements are shown in Figure 2 in the same way. The correla-

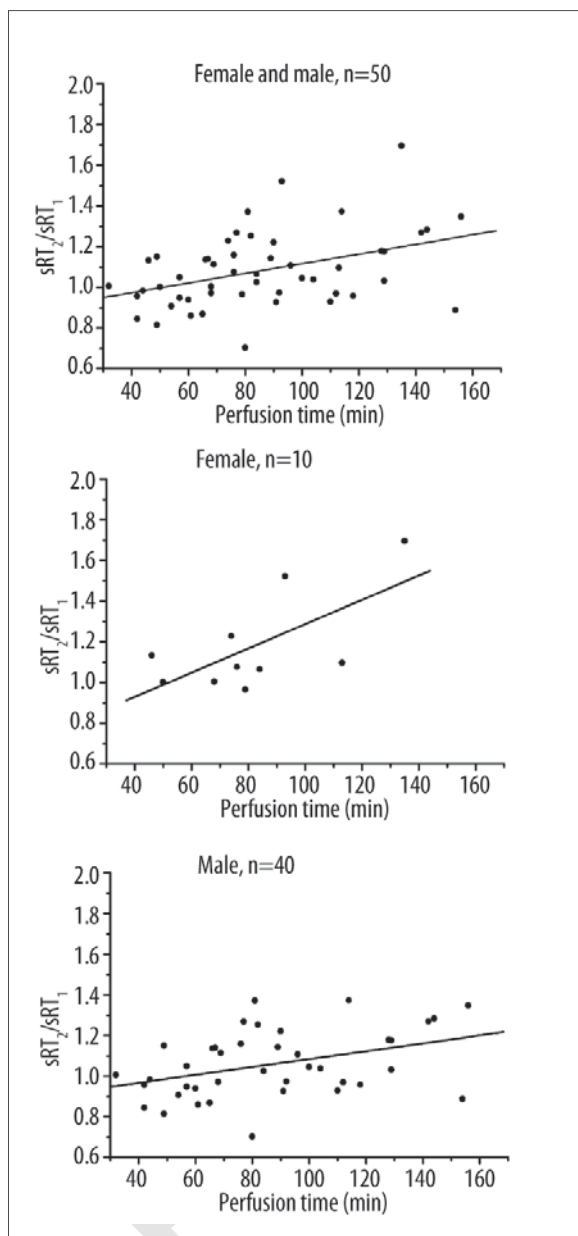


Figure 1. sRT_2/sRT_1 (the ratio of simple reaction time after and before the operation) versus perfusion time; scatter graphs with linear regression line in all the included patients and separately in women and men.

tion coefficients, the parameters of the regression model, and their levels of significance are detailed in Table 1. Note the relatively high constant parameter (b_0) and the negative correlation between aortic cross-clamp time and both sRT and cRT. Considering the slope of the regression lines, women are more susceptible to the harmful effects of longer perfusion time than men.

There were no statistically significant changes in mean sRT and cRT values before (sRT: 208 ± 54 s, cRT: 369 ± 59 s) and after (sRT: 229 ± 67 s, cRT: 392 ± 105 s) the surgery assessed in the total group or separately for the women and men by the Wilcoxon test. The reason for this might have been the inhomogeneous patient population, the wide range of CPB

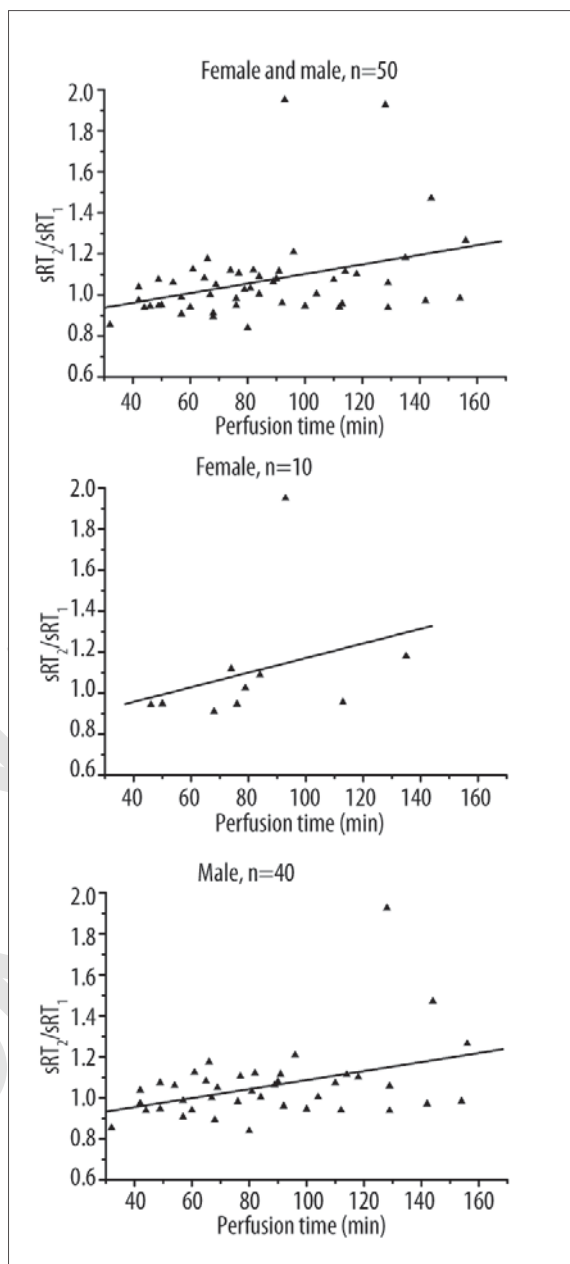


Figure 2. cRT_2/cRT_1 (the ratio of choice reaction time after and before the operation) versus perfusion time; scatter graphs with linear regression line in all included patients and separately in women and men.

time (32–156 s), and, consequently, the high standard deviation of reaction time changes.

The positive correlation between sRT_2/sRT_1 and cRT_2/cRT_1 was found to be weak (Figure 3). In certain individuals either sRT or cRT deteriorated, in some both, and in others neither. Improvement in reaction time was also observed in some patients.

DISCUSSION

The authors developed a bedside test which is clinically feasible, simple, and can be completed within 30 minutes to

Table 1. Correlation coefficients (*R*) and regression coefficients (*b*₀, *b*_{cross}, *b*_{perf}) in the regression model $y = b_0 + b_{\text{cross}} \times \text{crossclamp time} + b_{\text{perf}} \times \text{perfusion time}$ of the simple reaction time (sRT) and the choice reaction time (cRT) changes with their levels of significance.

sRT						
Sex	n	R	p	b ₀	b _{cross}	b _{perf}
F+M	50	0.5127	0.00008	0.8622	-0.0046*	0.0059**
F	10	0.8484	0.0116	0.8143	-0.0106*	0.0121**
M	40	0.4392	0.0190	0.8779	-0.0025	0.0039*
cRT						
F+M	50	0.3894	0.0210	0.8603	-0.0028	0.0045*
F	10	0.1418	0.5855	0.8803	-0.0055	0.0067
M	40	0.4224	0.0264	0.8578	-0.0020	0.0038*

p for *R*, **p*<0.05 and ***p*<0.01 for *b*_{cross} and *b*_{perf}; *n* – sample size; F – female; M – male.

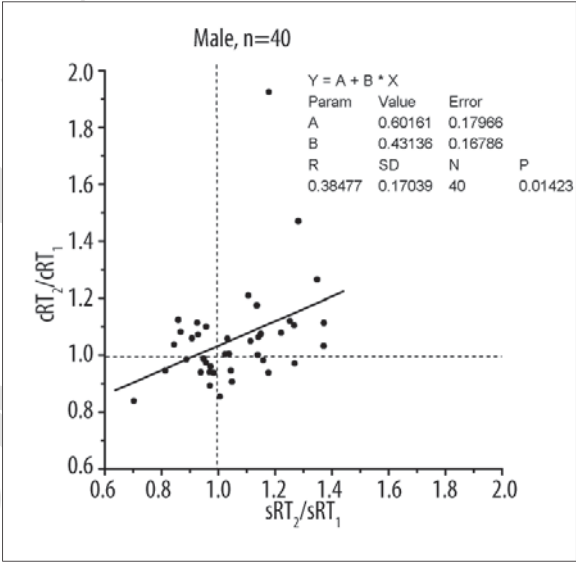
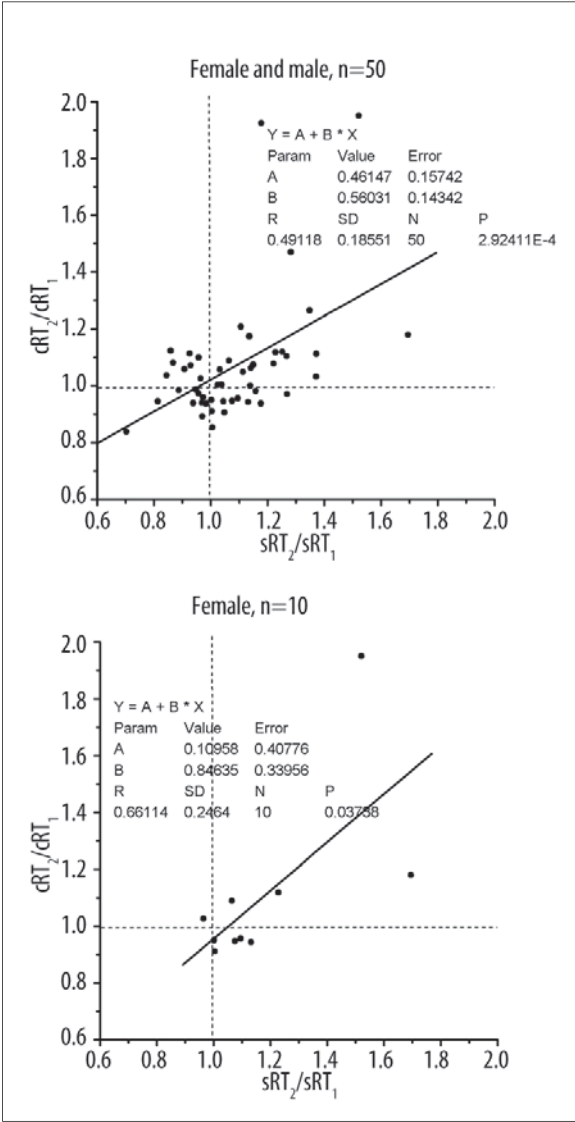


Figure 3. Relationship of *sRT*₂/*sRT*₁ and *cRT*₂/*cRT*₁ (the ratio of simple and choice reaction times after and before the operation) in all included patients and separately in women and men. Correlation coefficients (*R*) and significance levels of line-fitting (*p*) are indicated. The dotted unity lines representing no *sRT* or *cRT* changes are also shown.

determine *sRT* and *cRT* in patients who have undergone heart surgery. The automated statistical process makes the

analysis fast and easy. Considering the statistically non-significant differences in mean *sRT* and *cRT* in the population before and after the operation, regression and correlation to cross-clamp and perfusion time were analyzed. The explanation of the results is difficult due to the small sample size, inhomogeneous population, and the multifactorial etiology of brain injury associated with CPB reflected in the high standard deviation values, correlation coefficients, and the relatively high *b*₀ regression constant compared with the CPB time and cross-clamp time parameters. The *b*₀ parameter can be associated with other factors of brain injury, detailed in the introduction. This necessitates the extension of our measurements, including multivariate analysis (subgroups according to the comorbidities, age, type of operation, presence of aortic calcification, and aortic no-touch technique).

An unexpected issue is the shortening of reaction times after the operation. Its reason might be practice in using the method; however, it needs much more intensive training [33]. On the other hand, the partially discordant sRT and cRT changes oppose this theory. Another reason may be the improvement in cerebral perfusion postoperatively due to the successful operation. The elevated catecholamine levels and arousal in the postoperative course also may result in better reaction times. These hypotheses should be confirmed or discarded by further detailed studies.

The negative values of the cross-clamp time correlation coefficients (Table 1) are interesting, formally indicating a reduction in risk of brain injury; however, it is due to the multicollinearity of perfusion and cross-clamp time. Clinically, it may indicate that the relatively longer cross-clamp time within the perfusion time is probably associated with less comorbidity and better outcome (the need for less reperfusion time after releasing aortic cross-clamp because the heart recovers earlier).

The partially discordant changes in sRT and cRT (Figure 3) may reflect the physiological involvement and the lesion of different cerebral areas. Therefore, both of them should be measured.

The incidence of cerebral complications is directly proportional to increased age [3]. Elderly patients have a higher risk of brain damage occurrence associated with cardiac or non-cardiac surgeries [3,4,6], which calls for a reproducible and non-demanding method that easily measures and follows cerebral dysfunction and facilitates neurocognitive rehabilitation.

The cRT is the sum of the decision making (P300) and the motor process time [27]. Evaluating motor function by tremor analysis allows splitting the cRT, differentiating which one of its components is deteriorated. Concurrent heart rate variability analysis can assess autonomic nervous system involvement. Hence cognitive, motoric, and autonomic dysfunction can be simultaneously analyzed.

Taking into account our results and the need for a more extensive analysis, portable microcontroller-based equipment with USB or a Bluetooth interface to a PC is required. The data acquisition (sRT, cRT, tremor, ECG for heart rate variability analysis) would be performed without the PC connection. In a more comprehensive and larger (multicenter) study the correlation of sRT and cRT changes with neuropsychiatric tests, clinical outcome, or quality of life might be investigated. The ratio of discarded reaction time values or the ratio of errors during sRT and cRT measurement can also be assessed within the 30-minute examination. After further investigation, guidelines could be prepared for monitoring and supporting early postoperative neuropsychological abilities [34] and subsequent rehabilitation.

CONCLUSIONS

The reviewed sRT and cRT measuring system is reasonable in clinical practice and is not demanding to the patient as the entire measurement lasts for less than 30 minutes. The results show positive correlation of both sRT and cRT prolongation to perfusion time as a known risk factor of neu-

rocognitive injury. Women are more sensitive to a longer perfusion time. Further extensive studies are encouraged with an improved hand-held device to compare our method with neuropsychological and quality-of-life tests in a larger, stratified open heart surgery population.

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